

**Data from the Johnson Laboratory  
(University of Arizona) Should Not Be  
Used as Evidence of Cardiac  
Teratogenicity of TCE**

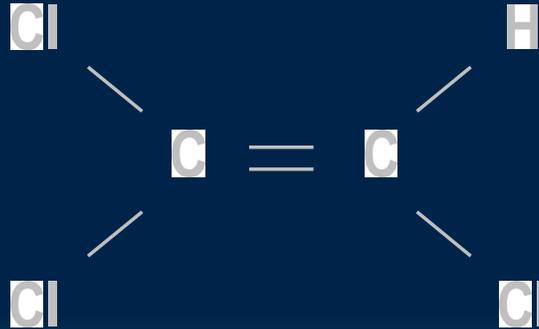
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**Exponent  
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# Trichloroethylene

(1,1,2-Trichloroethene; TCE; 113)



- Molecular Weight: 131.39
- Vapor Pressure: 0.011 psi @ 70°F
- Henry's Law Constant: 0.0011
- Log K<sub>ow</sub>: 1.99
- Water Solubility: 100 mg/L

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# Epidemiological Studies

Location (Reference)	Evaluated substance	Concentration
London, UK (Smith et al., 1999)	PM <sub>10</sub>	2-300 µg/m <sup>3</sup>
London, UK (Smith et al., 1999)	PM <sub>10</sub>	100 µg/m <sup>3</sup>
London, UK (Smith et al., 1999)	PM <sub>10</sub> (after adjusted exposure assessment)	100 µg/m <sup>3</sup>
London, UK (Smith et al., 1999)	PM <sub>10</sub>	Not indicated
London, UK (Smith et al., 1999)	PM <sub>10</sub>	1000 µg/m <sup>3</sup> at road level
London, UK (Smith et al., 1999)	PM <sub>10</sub>	Not indicated
London, UK (Smith et al., 1999)	PM <sub>10</sub> , nitrogen dioxide	Not indicated

PM<sub>10</sub> concentrations in the urban environment are higher than in the surrounding areas.

# Epidemiological Studies

Location (Reference)	Evaluated substance	Concentration
Tucson Valley, AZ (Goldberg et al., 1990)	TCE	6-239 ppb
Washington, DC (Gore et al., 1990)	PCB	10 ppb
Washington, DC (Gore et al., 1990)	PCB (polychlorinated biphenyls were also present)	100 ppb
Washington, DC (Gore et al., 1990)	PCB	Not indicated
North Wales, UK (general investigation)	Polychlorinated biphenyls	1000 ppb of total PCB
New Orleans, LA (Gore et al., 1990)	Polychlorinated biphenyls	Not indicated
Washington Metropolitan Corridor (Gore et al., 1990)	Polychlorinated biphenyls, polycyclic aromatic hydrocarbons	Not indicated

PCB concentrations in the public drinking water in Washington DC significantly lower.

# Tucson Valley, AZ

- ▶ 1980s and 1990s dominated by the technology sector in 1990
- ▶ Environmental Policy began in the 1990's
- ▶ Environmental movement that continues with a significant trend toward policy toward to regulate business in the environmental sector since 2000.
- ▶ Green and sustainable development

# Goldberg et al., 1990 study

- ▶ Investigated the genetic relationship with a DNA marker in the population in which different degree of methylation influences (H and h alleles)
- ▶ Study results
  - 0.000000 alleles in individuals assigned methylation
  - 0.000000 alleles in individuals assigned methylation
  - 0.000000 alleles in individuals assigned methylation
  - -0.000000 alleles with DNA marker in individuals assigned in the DNA
  - Methylation status of methylation sites, with all DNA in human DNA assigned to 0.000000

# Limitations of Goldberg et al., 1990 Study

- ▶ Absorption of various pollutants and other toxic substances
- ▶ Development of diseases and other conditions
- ▶ Long-term health effects of stress
- ▶ Low- and high-dose effects that occur in human and other naturally exposed
- ▶ The developmental rates of stress in -

## Mammalian Studies Suggesting a Positive Correlation Between TCE and CHD

Reference	Exposure route	TCE exposures	Conc @ ↑ CHD	Animal model and N
Dawson et al., 1993	Inhalation gage Ingested pregnancy	10 ppm 1000 ppm	1000 ppm*	Myogaes Mating rats N=10-100/group
Dawson et al., 1993†	Maternal exposure to Breeding males Breeding pregnancy	1.0 ppm 1000 ppm	1000 ppm*	Myogaes Mating rats Offspring not reported
Dawson et al., 1993†	Maternal exposure to Breeding males Breeding pregnancy	0.0 ppm 0.05 ppm 1.0 ppm 1000 ppm	- 0.05 ppm - 1000 ppm	Myogaes Mating rats (Foster) N=10-100/group

\* Statistically significant as a per-foetus basis

† Statistically significant as a per-litter basis

‡ Data presented in Dawson, 1993 were again presented in Johnson et al., 2003; Also, both studies use the Dawson method of dissection.

## Mammalian Studies Suggesting a Positive Correlation Between TCE and CHD

Reference	Exposure route	TCE exposures	Conc @ ↑ CHD	Animal model and N
Dawson et al., 1993	Intrauterine pump throughout pregnancy	0.0 ppm 1.0 ppm	1.00 ppm*	Organic Solving rats N=10-100/group
Dawson et al., 1993 <sup>ii</sup>	Maternal exposure to drinking water during pregnancy	1.0 ppm 1.00 ppm	1.00 ppm*	Organic Solving rats Histology not reported
Dawson et al., 1993 <sup>ii</sup>	Maternal exposure to drinking water during pregnancy	0.0 ppm 0.01 ppm 1.0 ppm 1.00 ppm	- 0.01 ppm - 1.00 ppm	Organic Solving rats (female) N=10-100/group

\* Statistically significant as a per-lesion basis

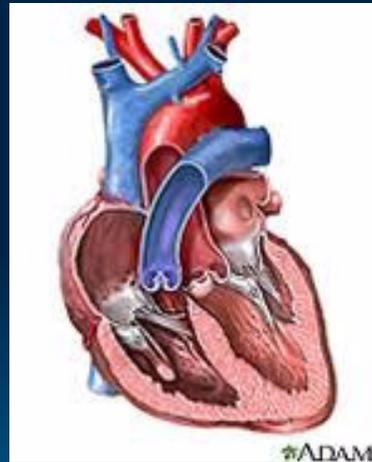
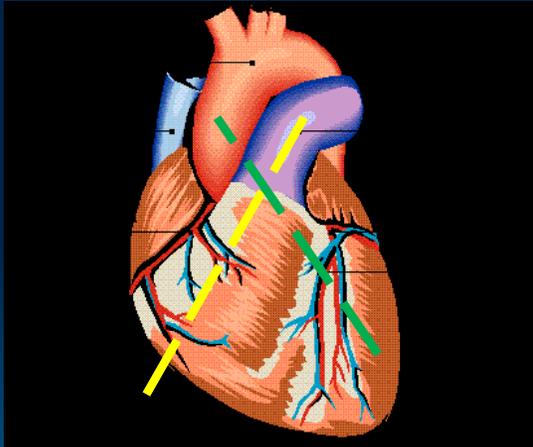
ii Statistically significant as a per-lesion basis

ii Data presented in Dawson, 1993 were again presented in Johnson et al., 2003; Also, both studies use the Dawson method of dissection.

# Problems with Methodology

- ▶ Most of studies have significant problems with validity
- ▶ Most of studies used data on educational well-being
  - ⊗ Studies of illness and reported
- ▶ Measurement problems of illness are many
  - ⊗ Mental - 100 different questions (1999)
  - ⊗ All studies illness are 0-100 mental illness (1999)
- ▶ In Denmark (1999), some major sources of evidence are unreliable
- ▶ Mental is now mental for consulting boards

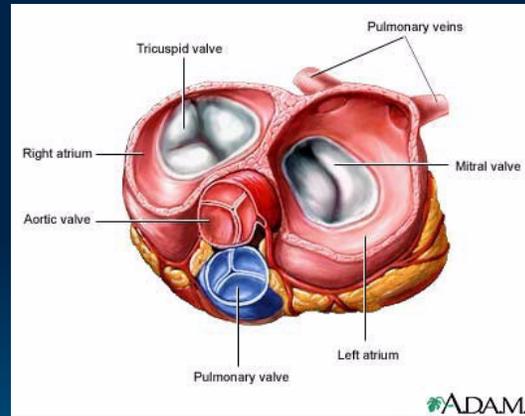
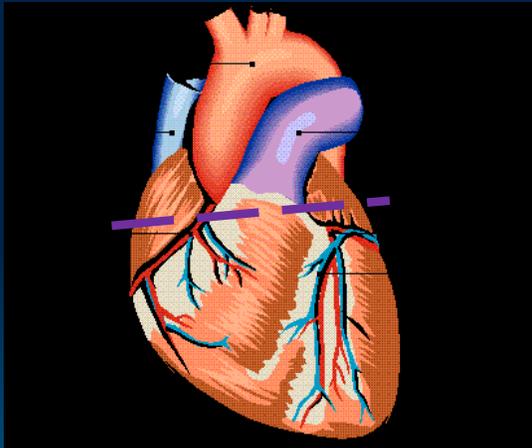
# Standard Method of Heart Evaluation



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# Dawson Method of Heart Evaluation



Abnormal conditions with subsequent dilation (e.g., swelling of heart in the case of coronary artery disease, use of drugs)

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# Problems with Results

- ▶ Good actions are being done
  - Being managed with discipline
- ▶ Challenges are being done
- ▶ Processes are being done
- ▶ The financial data is being done

# Comparison of Dawson (1993) with Johnson (2003)

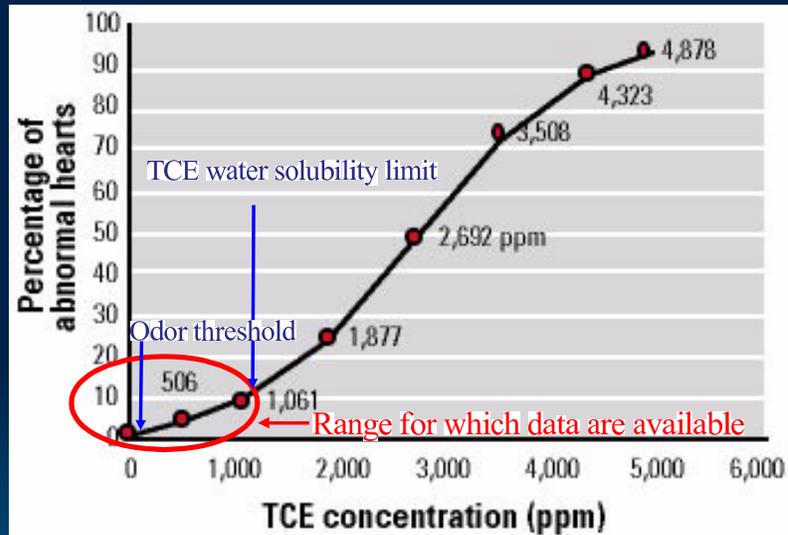
Method/Measurement (Reference et al. 1993)	1993 Cases		Method/Measurement (Reference et al. 2003)	2003 Cases	
	1,0 year	1,000 year		1,0 year	1,000 year
Abnormalities (Reference et al. 1993)	0	0	Abnormalities (Reference et al. 2003)	0	0
Abnormalities (Reference et al. 1993)	1	0	Abnormalities (Reference et al. 2003)	1	0
Abnormalities (Reference et al. 1993)	1	0	Abnormalities (Reference et al. 2003)	1	0
Abnormalities (Reference et al. 1993)	4	7	Abnormalities (Reference et al. 2003)	4	7
Abnormalities (Reference et al. 1993)			Abnormalities (Reference et al. 2003)		
Abnormalities (Reference et al. 1993)	0	1	Abnormalities (Reference et al. 2003)	0	1
Abnormalities (Reference et al. 1993)	0	2	Abnormalities (Reference et al. 2003)	0	2
<b>No. with abnormal hearts</b>	<b>9</b>	<b>11</b>		<b>9</b>	<b>11</b>
<b>No. fetuses examined</b>	<b>181</b>	<b>105</b>		<b>181</b>	<b>105</b>

Method/Measurement (Reference et al. 1993)

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# Predicted Dose-response Curve

Based on data from University of Arizona Goldberg/Johnson/Dawson laboratory with the exception of the Fisher et al., 2001 study



Goldberg et al., 2000: "A weight analysis of the frequency of abnormal hearts in each group was done to identify the dose-response curve. Weight analysis was performed with logit transformation and the actual response rate calculated from the odds ratio in the weight group."

## All animal data reporting heart defects with TCE come from one laboratory

- ▶ Data from that lab were accumulated over the years (between 01/01/00, January 01 of 2000, to 01/01/03)
- ▶ Collaboration in study design and reporting with the investigators at Data Evaluation of that
- ▶ Major ethical and regulatory violations of animal subject research for the purposes stated, which almost caused the

# Animal Studies Which Do Not Indicate a Positive Association Between TCE and CHD

## TCE Inhalation:

Reference	Exposure route	Vapor TCE Conc	Animal Model/N
Watanabe et al., 1988	Subtotal Inhalation of vapors 8 Working Days pregnancy	500 ppm	SD rats, 50-100mg/kg Dose 0.0001 mg/kg 0-10-100mg/kg
Watanabe et al., 1988	Subtotal Inhalation of vapors, 8 days, at 10 days and 20 days pregnancy (-10 days was 500 ppm)	1000 ± 500 ppm	Long Evans rats 0-100mg/kg
Wardle et al., 1981	Subtotal Inhalation of vapors for 8-8 Working Days pregnancy (0-1-10 only 1-100 mg/kg)	500 ppm	SD and Wistar rats 0-10-100mg/kg Dose 0.0001 mg/kg 0-10-100mg/kg
Wardle et al., 1981	Subtotal Inhalation for 8 Working Days pregnancy (0-1-10)	100 ppm	Wistar rats/kg 0-10-100mg/kg
Wardle et al., 1981	Subtotal Inhalation 8 Working Days 0-1-10	50, 100, 500 ppm	SD rats, 100mg/kg

# Animal Studies Which Do Not Indicate a Positive Association Between TCE and CHD, Continued

## TCE Oral exposure:

Reference	Exposure route	TCE Conc.	Animal Model/N
Wallerstein Neurology Magazine, 1988	Daily subcutaneous and gavage during pregnancy	100, 200, and 400 mg/kg/day during	-20 Sprague Dawley rats/day
Wallerstein Neurology Magazine, 1988	Daily subcutaneous and gavage during pregnancy	10, 100, and 400 mg/kg/day during	-20 Sprague Dawley rats/day
Woolley and Wahlman, 1988	Daily subcutaneous and gavage on DD 1-3, 5-10, and 11-15	10 and 100 mg/kg/day	-10 Sprague Dawley rats/day
Wallerstein et al., 1988	Daily subcutaneous and gavage on 5-15	100 mg/kg/day during	10 Sprague Dawley rats per group

1000 Sprague Dawley Rats in Groups 1000, 1000 and 1000, 1000

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# Animal Studies Which **Do Not** Indicate a Positive Association Between TCE and CHD, Continued

## TCE Oral exposure:

Reference	Exposure route	TCE Conc.	Animal Model/N
Wallace/Walsh/Myers, 1999	Daily maternal oral gavage during pregnancy	100, 200, and 500 mg/kg/day	-20 Sprague Dawley rats/group
Wallace/Walsh/Myers, 1999	Daily maternal oral gavage during pregnancy	10, 100, and 500 mg/kg/day	-20 Sprague Dawley rats/group
Wooly and Williams, 1999	Daily maternal oral gavage on GD 1-5, 6-10, or 11-15	10 and 500 mg/kg/day	-10 Sprague Dawley rats/group
Fisher et al., 2001	Daily maternal oral gavage GD 6-15	500 mg/kg/day TCE=1	20 Sprague Dawley rats per group

1000 Sprague Dawley Rats in Groups of 100, 1000 and 10000, 1999

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# Trichloroethylene, Trichloroacetic Acid, and Dichloroacetic Acid: Do They Affect Fetal Rat Heart Development?

Jeffrey W. Fisher,<sup>1</sup> Stephen R. Channel,<sup>1</sup> Jeffrey S. Eggers,<sup>1</sup> Paula D. Johnson,<sup>2</sup> Kathleen L. MacMahon,<sup>1</sup> Chuck D. Goodyear,<sup>3</sup> Gregory L. Sudberry,<sup>1</sup> D. Alan Warren,<sup>1</sup> John R. Latendresse,<sup>4</sup> and Linda J. Graeter<sup>4</sup>

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# Dose Groups and Sizes from Fisher et al, (2001)

**TABLE 1**  
Pregnant rat treatment groups and the number of dams  
and fetuses per dose group

Treatment group	Dose (mg/kg/day)	Number of dams	Number of fetuses
Trichloroethylene	500	20	292
Trichloroacetic acid	300	19	269
Dichloroacetic acid	300	20	303
Retinoic acid	15	12	160
Soybean oil—control	—	25	378
Water—control	—	19	275

# Advantages of Fisher et al (2001)

- ▶ Responses indicated that participants felt they had demonstrated their knowledge as well as a positive attitude
- ▶ Most students indicated that their attitude towards mathematics had been reinforced
- ▶ Satisfaction was indicated

# How to Decide

(Watson et al, 2006)

The logo for Exponent, featuring the word "Exponent" in a serif font with a registered trademark symbol, set against a dark blue rectangular background. The background of the slide also features faint, concentric circular patterns in shades of blue and white, resembling ripples in water, located in the lower right quadrant.

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## Does TCE cause a specific type of CHD?

Reference	Concentration of evaluated substance	Study type	Predominant type of CHD reported
Wilkens and Wilson, 1988	No specific concentrations of congenital defects; study examines effect of 1,1,1-trichloroethane	Epidemiological; Case-control	<ul style="list-style-type: none"> <li>Ventricular Septal Defect (VSD; specific type not indicated)</li> </ul>
Smith et al., 1988	100-1,000 mg/kg/day trichloroethylene	Animal study; Case-control	<ul style="list-style-type: none"> <li>Levocardia</li> <li>VSD (specific type not indicated)</li> </ul>
Smith et al., 1988	10-1,000 mg/kg/day of trichloroethylene (TCE)	Animal study; Case-control	<ul style="list-style-type: none"> <li>Levocardia</li> <li>Defects between ascending aorta and right ventricle</li> <li>VSD (specific type not indicated)</li> </ul>
Wright et al., 1988	1,000-2,000 mg/kg/day TCE	Animal study; Case-control	<ul style="list-style-type: none"> <li>VSD type I</li> <li>VSD type II</li> </ul>

# Predominant types of developmental mechanisms

- ▶ Cellular migration
- ▶ Extracellular matrix formation
- ▶ Stem cell generation
- ▶ Regulated growth
- ▶ Cell death
- ▶ Immune cells

# Distribution of CHD types and the Developmental Process Disturbed in the General Population

Type of Congenital heart defect	% CHD patients with this defect	Developmental Process Disturbed
Transposition of the great vessels	10-20%	Cell migration, cell death, endocardial matrix formation, valve development
Patent ductus arteriosus	0-10%	Cell migration
Development of the great vessels	10-20%	Cell migration
Septal defects	0-10%	Endocardial matrix formation
Development of the valve	0-10%	Development
Septal defects	0-10%	Development

Information from this table was obtained from studies published by the American Heart Association (2000) and Hoffman and Kaplan, 2002.



# Conclusions

- ▶ The aggregate results of the data do not support the concept that the program increases the rate of job loss
- ▶ These data could be used to question conclusions that the use of the program reduces the rate of job loss. The program is not associated with significantly higher rates of job loss that are not related to expected organizational changes